REMARKS

Amendments to the specification

The specification was objected to for including hyperlinks. As requested, each hyperlink has been deleted.

Amendments to the claims

Claim 40 has been amended to specify that the modified allergen lacks an IgE binding epitope of the wild-type allergen. Claims 45-47 have been added. Claim 45 is a dependent claim that specifies that the dead *E. coli* was heat-killed (e.g., see [0047], [0057] and Examples 1 and 3 of the specification for support). Claim 46 is a dependent claim that specifies that the dead *E. coli* was killed by chemical treatment. Claim 47 further specifies that the dead *E. coli* was killed using a chemical selected from the group consisting of iodine, bleach, ozone, and alcohols (e.g., see [0047] of the specification for support).

No new matter is being added.

Rejection for lack of enablement

Claims 34-36 and 38-44 were rejected for lack of enablement. Essentially, the Examiner argues that the invention was so unpredictable at the time of filing that a skilled person could not have made and used the claimed invention without an undue amount of experimentation. This rejection is respectfully traversed; reconsideration and withdrawal is requested.

The examiner's argument is based on three alleged sources of unpredictability. First, the examiner argues that the immunological properties of the claimed compositions were unpredictable at the time of filing (see page 3 of the office action). Second, the examiner argues that the expression of allergens in *E. coli* was unpredictable at the time of filing (see pages 3 and 5 of the office action including citation to Kleber-Janke et al.). Third, the examiner argues that allergen mutations that reduce IgE binding were also unpredictable (see pages 4-5 of the office action including citations to Skolnick et al., Fasler et al., Burks et al. and Stanley et al.). These three issues are addressed in turn below.

Immunological properties

In arguing that the immunological properties of the claimed compositions are unpredictable, the examiner points to the examples in the specification (specifically, Examples 3 and 4) and attempts to argue that these examples show unpredictability because different results were obtained with different allergens. Applicant respectfully submits that the examiner does not accurately describe the contents of the examples she cites.

As discussed in the specification, microorganisms such as *E. coli* tend to produce Th1-type (i.e., non-allergic) immune reactions in individuals. In contrast, allergens such as the peanut allergens Ara h 1, 2 and 3 tend to produce Th2-type (i.e., allergic) immune reactions. Th1-type immune reactions and Th2-type immune reactions are mutually inhibitory. One aspect of the present invention is the recognition that, by administering allergens in the context of microorganisms such as *E. coli*, it might be possible to cause a recipient individual to mount a Th1-type immune reaction to the administered allergen, and therefore to suppress any Th2-type reaction to that allergen (see specification, for example, [0041]).

The specification describes the administration of *E. coli* cells that contain the peanut allergens Ara h 1, 2 or 3 to mice. According to the Examples, high levels of IgG2a (indicative of a Th1-type response) were observed for *both* Ara h 2 and Ara h 3. High levels of IgG1 (indicative of a Th2-type response) were also observed for Ara h 2. Antibody levels were not high enough for Ara h 1 to detect whether Th2-type or Th1-type responses were occurring. Thus, the specification *exemplifies* initiation of a Th1-type immune reaction to peanut allergens Ara h 2 and Ara h 3 expressed in *E. coli*. It is true that evidence of a Th2-type reaction was also observed for Ara h 2, but that was explained as resulting from released protein which, obviously, would be expected to induce a strong Th2 response.

This simple finding is incredibly powerful. Peanut allergy is one of the most severe allergies known to man. The present inventors *demonstrated* that it is possible to cause peanut allergens to induce a non-allergic reaction merely by presenting them in the context of *E. coli* cells. The present inventors also *explained* why deviations were observed for Ara h 1 (lower expression) and Ara h 2 (released protein). Those of ordinary skill in the art, armed with these teachings, would have recognized that the immunological properties of the inventive compositions are, in fact, reasonably predictable.

Expression of allergens in E. coli

On page 5 of the office action, the examiner cites Kleber-Janke et al. as teaching "the unpredictability of bacterial *E. coli* expressing [sic] allergen such as peanut allergens Ara h 1, Ara h 2, Ara h 5 and Ara h 6." Applicant respectfully submits that the examiner is reading more into this reference than a person of ordinary skill would have in light of applicant's teachings.

Kleber-Janke et al. describe two systems for expressing Ara h 1, 2, 5 and 6. One system uses conventional *E. coli* cells while the other uses *E coli* cells that have been engineered to overproduce tRNAs for "rare" *E. coli* codons. Of note, the engineered cells appear to have been purchased from Stratagene at or around the time applicant filed their priority application (i.e., March 2000, see also Carstens et al. (1999) which is cited as Ref. 18 by Kleber-Janke et al.). Kleber-Janke et al. found that expression of Ara h 1, 2 and 6 was nearly 100 fold greater in the engineered cells (while expression of Ara h 5 was unchanged). This difference resulted from the higher proportion of rare *E. coli* codons in Ara h 1, 2 and 6 than in Ara h 5. Thus, the increased expression of Ara h 1, 2 and 6 observed by Kleber-Janke et al. was *exactly* what would have been expected given the gene sequences (e.g., see comment by Kleber-Janke et al. on page 422: "Referring to these facts, the translational problems with the mRNAs of the three peanut allergens Ara h 1, Ara h 2, and Ara h 6 were to be expected").

Far from demonstrating unpredictability of protein allergen expression, Kleber-Janke et al. shows that at the time of filing, researchers of ordinary skill had at their disposal a variety of tools that could be employed to *predictably* modulate expression as desired. In fact, Kleber-Janke et al. themselves note on page 422 that at the time the present application was filed there were at least three relevant strategies for overcoming this specific cause of low expression, namely:

- [using] a host containing a plasmid with the appropriate tRNA [citing Refs. 10, 24 and 25 from 1989, 1995 and 1996, respectively];
- [synthesizing] the gene to replace rare codons with frequently used codons [citing Ref. 26 from 1989]; or
- [using] *E. coli* hosts that carry extra copies of the argU tRNA gene [citing Ref. 18 from 1999].

A skilled person would have been equally aware of methods for increasing allergen expression in other contexts. Indeed, as noted on page 12 of the present application, *E. coli* was possibly the most well-studied bacterium at the time of filing. Thus, a range of routine methods for optimizing protein expression in *E. coli* were known by 2000 (e.g., see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989 and the more recent Ausubel et al. *Current Protocols in Molecular Biology*. Wiley and Sons. New York. 1999 that were incorporated by reference).

It is further worth noting that the present specification provides detailed guidance for expressing very high levels of peanut protein in wild type *E. coli*. Those of ordinary skill, reading the present application, would for instance be taught how to produce > 10 mg Ara h 2 from a culture of wild type *E. coli*, even without employing available enhancements such as those describes by Kleber-Janke et al.

Peanut allergen mutations

The claimed compositions comprise dead *E. coli* cells that contain modified allergens with reduced IgE binding. The examiner argues that it would require undue experimentation to make any suitably modified allergen because the selection of mutation(s) would be too unpredictable. To support this argument, the examiner points in part to applicant's own peptide mutational studies with peanut allergens Ara h 1 (Burks et al.) and Ara h 2 (Stanley et al.). Specifically, the examiner jumps on the fact that *some* of the Ara h 1 and Ara h 2 mutations that applicant tested failed to reduce IgE binding or even increased IgE binding (see pages 4-5 of office action). According to this examiner, these "failures" render the mutational step so unpredictable that it would require undue experimentation to practice the claimed invention. In fact, in office actions for related cases, this examiner has argued that the mutational step is rendered so unpredictable by these "failures" that a skilled person would have been unable to make a suitably modified allergen without actually being given the amino acid sequence of the modified allergen. This argument is absurd for several reasons.

First, it disregards the fact that Burks et al., Stanley et al. and the current application describe a vast number of Ara h 1, 2 and 3 mutations that *did* reduce IgE binding (e.g., see the numerous mutations that are listed in the Tables and Examples of U.S. Serial No. 09/141,220 that is incorporated by reference in [0069]). Thus, the present application explicitly enables the

making of a significant number of species within these genus'. These "successes" would have weighed heavily against the "failures" that the examiner refers to – the level of predictability can only be assessed by considering both. The fact that the prior art and the current application demonstrate a frequency of "successes" that far outweighs the frequency of "failures" would have clearly indicated to a person of ordinary skill that the mutational step was far more predictable than the examiner suggests.

Second, the examiner's argument does not take into account the nature and amount of experimentation that would actually be required to identify suitable mutations that are not explicitly described in the application. In particular, as set forth in *Wands*, when the starting materials are readily available and the experimentation is of a *routine* nature then the level of experimentation is not undue. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). This is true even if a significant amount of experimentation would be required. *Id.*

Here, as in *Wands*, the starting materials including numerous allergen sequences were available to the public at the time of filing (e.g., see Appendix A on pages 41-54 which includes GenBank accession numbers and/or references for all allergens that were known at the time of filing; for a number of these IgE epitopes were also known and described in the cited references). For the peanut allergens Ara h 1, 2 and 3 the specification further describes a number of exemplary sites within these IgE epitopes that have been shown to cause a reduction in IgE binding when mutated (e.g., see the numerous mutations that are listed in the Tables and Examples of U.S. Serial No. 09/141,220 that is incorporated by reference in [0069]). Methods of preparing peptides or full length proteins that have been mutated with different amino acids and/or at different sites, and methods of screening these for reduced IgE binding were also comprehensively described in the specification. Most importantly, these preparation and screening steps were *mechanical* in nature and *routine* in the art at the time of filing. In fact, at the time of filing, a skilled person could have readily automated these steps. The steps involved in this case are reminiscent of the steps that were involved in preparing the antibodies of *Wands*. There, the Court found that, although the technology involved preparing and then screening hybridomas to determine which, if any, secreted antibodies with the desired characteristics, "[p]ractitioners of the art [were] prepared to screen negative hybridomas in order to find one that makes the desired antibody." The Court did not quantify the required likelihood of success, but noted that even a success rate as low as 2.8% would not necessarily require a conclusion of

undue experimentation! Thus, in *Wands*, there was a high probability that future efforts to generate antibodies within the claims would *not* succeed. However, the *Wands* inventors had demonstrated that success was achievable, and the steps required to repeat this success though laborious were routine. In this case, applicant has demonstrated that success can be achieved with a success rate that is at least as great as in *Wands*[1]; the steps required for others to repeat this success with different mutations using the same or different allergens were routine. The present case need only meet the enablement standard that was set in *Wands*. Applicant respectfully submits that the standard has been met.

Finally, the examiner has previously suggested in related cases that applicant could only have enabled the claimed invention by actually describing the amino acid (and cDNA) sequences of *every* possible modified allergen with reduced IgE binding. Applicant respectfully submits that the standard proposed by the examiner would equate enablement with reduction to practice. For good reason, this is simply not the law. The whole point of the enablement requirement is that it allows patent applicants to claim inventions that are commensurate in scope with their *contribution* to the art. The examiner has argued that applicant's contribution is limited to the specific mutations that are described in the specification. This is clearly unreasonable and unsupported by the facts of this case. Any skilled person would recognize that applicant's contribution to the art was much broader than this. Specifically, the skilled person would immediately realize that other suitable mutations exist and that these could be determined by routine experimentation. Under *Wands*, no more is required in order to fully enable the claimed invention.

Interestingly, the examiner cited *Fisher* for the inverse relationship that exists between enablement and predictability. *In re Fisher*, 166 USPQ 18 (CCPA 1970). However, the examiner failed to note that in *Fisher* the Court also considered whether a patent applicant should be entitled to claim inventions that are obtainable from his teachings plus ordinary skill. The court answered this in the affirmative:

[1] The results in Example 2 of U.S. Serial No. 09/141,220 demonstrate that for Ara h 1, 2 and 3 the success rate was consistently greater than 27% (Tables 4-6 show that 58/220; 35/100 and 16/60 single mutations resulted in less than 1% of IgE binding as compared to wild-type).

> "It is apparent that such an inventor should be allowed to dominate the future patentable inventions of others where those inventions were based in some way on his teachings. Such improvements, while unobvious from his teachings, are still within his contribution, since the improvement was made possible by his work. It is equally apparent, however, that he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. 112." *Id. at 24.*

Thus, in contrast to some of the examiner's arguments, it is quite clear that the courts recognize that patent applicants should not be limited to claiming what they have explicitly disclosed. Instead, patent applicants should be entitled to claims that are commensurate with the scope of their contribution even if these reach invention that are *unobvious* from the explicit teachings. For all of these reasons, applicant respectfully requests that the examiner reconsider and withdraw the rejection of claims 34-36 and 38-44 for lack of enablement.

Rejection for lack of written description

Claims 34-36 and 38-44 were rejected for lack of written description. This rejection is also respectfully traversed; reconsideration and withdrawal is requested.

The Examiner argues that applicant was not in possession of the claimed invention at the time of filing because "the specification does not describe the structure corresponding with function of *any* modified allergen in the claimed composition" (see page 6 of office action, emphasis added). Specifically, the examiner argues that "[w]ithout the amino acid sequence of any modified allergen in the claimed compositions, the specification merely ask [sic] one of skilled [sic] in the art to come up with the structure of the modified allergen in the dead *E. coli* for the claimed composition."

The examiner reaches these conclusions by limiting her analysis to the specific species that applicant *reduced to practice* and *explicitly recited* in the specification, i.e., the *modified* peanut allergens Ara h 1, 2 and 3. This is clearly not the legal standard under the written description requirement nor should it be. Indeed, the question is not "did applicant *reduce to practice* a representative number of species" but "was applicant in *possession* of a representative number of species." Any written description analysis must therefore take into account *all* species that are described in the application including those that were not reduced to practice.

While modified allergens other than modified peanut allergens were not reduced to practice these species were described in the specification. Notably, the specification explicitly stated that other modified allergens could be used in inventive compositions (e.g., see [0017], [0019], [0062]-[0072] and Appendix A). Indeed, as stated in the specification the invention encompasses the fact that any modified allergen with reduced IgE binding will present a reduced risk of causing an allergic or anaphylactic response in individuals that are treated with vaccines containing the inventive compositions (e.g., see [0069]). As noted above, for a number of these allergens IgE binding epitopes were already known. For others they could be identified using routine methods (e.g., see page 7, line 31 to page 8, line 8 and Example 1 of incorporated application U.S. Serial No. 09/141,220, see [0069]). It was also well known in the art that a many IgE binding epitopes share a common structural motif – namely a short linear stretch of amino acids within the overall allergen sequence (e.g., see Tables 1-3 of incorporated application U.S. Serial No. 09/141,220). The specification also describes sequence modifications within IgE sites (e.g., see Examples 2-3 of U.S. Serial No. 09/141,220), and identification of modifications that reduce IgE binding (e.g., see Examples 2-3 of U.S. Serial No. 09/141,220).

And, of course, the specification provides evidence that the inventive strategy successfully produced modified peanut allergens with reduced IgE reactivity. The teachings and guidance provided by this success are far-reaching. As discussed above, peanut allergy is one of the most potent allergies. A person of ordinary skill in the art would immediately understand the exciting implications of the inventive exemplification of reduced-allergenicity peanut allergens: if it works for peanuts, it will work for other allergens.

The claimed allergens are all proteins; sensitized individuals are exposed to them all by the same route (i.e., ingestion); they are all readily modified according to the same techniques, and those with reduced allergenicity are identified in the same manner. Reading the present specification, those of ordinary skill in the art will immediately appreciate that modified allergens with reduced allergenicity, according to the present claims, exist, and can readily be made according to the teachings of the specification. In other words, those of ordinary skill in the art will immediately appreciate that the inventors were *in possession of* the claimed invention.

All of this information explicitly set forth in the specification, combined with the potent demonstration of success with the most challenging allergens, clearly put the public on notice

that the inventors were in possession of the invention to the full scope of the present claims. Appellant appreciates that certain court decisions, including *University of California v. Eli Lilly and Co.* have been interpreted to stand for the proposition that, in certain cases, nucleic acid or protein molecules cannot be properly described in a patent specification without explicit recitation of sequence information. However, this is not such a case. First, significant sequence information *is* provided for this case. Furthermore, a determination of whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by those skilled in the art *at the time that the invention was filed. In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). In *University of California v. Eli Lilly and Co.*, the patent applications in issue were filed in 1977 and 1979; the present application was filed 20 years later. A lot happened in the intervening 20 years. Automated sequencing, synthesis and screening technologies were developed; PCR was invented; a variety of techniques for disrupting or otherwise mutagenizing a nucleic acid sequence were standardized. Mechanical application of a "Sequence Listing or bust" rule vitiates the very purpose of the *Lily* ruling, which was to ensure that the scope of patent claims was commensurate in scope with the contribution.

A claim limited to the particular substitutions that the inventors happened to have made prior to filing their patent application is virtually useless. Anybody of ordinary skill in the art could prepare a modified allergen that falls outside the scope of the claim but still embodies the spirit, scope, and teachings of applicant's contribution. If the legal standard of written description in fact required verbatim recitation of every possible useful sequence, as asserted by the examiner, patent applicants would be forced to perform useless and wasteful experiments (potentially endlessly) merely to ensure that they could protect their contributions. Such a standard would eviscerate the patent system. The examiner's rejection of claims 34-36 and 38-44 for lack of written description should be removed.

Rejection for lack of definiteness

Claim 40 was rejected under 35 U.S.C. § 112, second paragraph for being indefinite. Specifically, the examiner argued that the term "portion" is indefinite because it could be as little as 1 amino acid or could be as much as 100 amino acids. Applicant respectfully disagrees with the examiner. Claim 40 is designed to cover modified allergens that lack one or more IgE binding epitopes as compared to the wild-type allergen. Claim 40 therefore requires that the

removed "portion" of the wild-type sequence include an IgE binding site. A person of skill would be able to compare a modified allergen sequence with a wild-type sequence and determine whether the differences between the two correspond to one or more IgE binding sites. No more is required in order to satisfy the definiteness requirement. However, solely in order to expedite prosecution of this case towards allowance, applicant has amended claim 40 to specify that the modified allergen lacks an IgE binding site. The examiner's rejection of claim 40 for lack of definiteness should be removed.

Rejection of claims 34-36, 38-40 and 42-44 for obviousness

Claims 34-36, 38-40 and 42-44 were rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,888,799 ("the '799 patent") in view of WO 99/38978 ("the '978 publication") and Yeung et al. ("Yeung"). The examiner cites the '799 patent for teaching a composition comprising live bacteria such as *E. coli* that contain any allergen and a pharmaceutically acceptable carrier (see page 8 of office action). The examiner then cites the '978 publication for teaching live *E. coli* that contain a modified peanut allergen Ara h 1, 2 or 3 (see page 9 of office action). Finally, the examiner cites Yeung for teaching that heat-killed *Listeria monocytogenes* acts as an adjuvant that can bias an allergic reaction towards a Th1-type response (see page 9 of office action). The examiner then argues that it would have been obvious to produce the claimed invention by (a) substituting the live *E. coli* of the '799 patent with the live *E. coli* of the '978 publication; and then (b) heat-killing the *E. coli* as taught by Yeung. This rejection is respectfully traversed; reconsideration and withdrawal is requested.

Regarding substitution step (a), Applicant respectfully notes that the '978 publication relates to peanut allergens and goes to great lengths to highlight the potentially lethal consequences of accidental exposure to these anaphylactic allergens (e.g., see page 13, line 33 to page 14, line 11). In contrast, the '799 patent relates for the most part to methods of expressing isolated microbial antigens (e.g., antigens from infectious bacteria or viruses) in avirulent microbial vehicles. These so-called "subunit vaccines" are designed to *minimize* unwanted immune reactions while providing protection against the infectious pathogens. This is highlighted for example when the '799 patent highlights that the vaccine "does not have antigenic material associated with it that is capable of causing undesirable antibody-antigen reactions" (see column 2, lines 50-55). In addition, even though the expressed antigens in the

cited references are sometimes described in general terms that include allergens, anaphylactic allergens are never discussed. In fact, the only time that specific allergens are mentioned, reference is made to the non-anaphylactic pollens and animal danders (see column 9, line 65). Appellant respectfully submits that the potent immunological nature of anaphylactic peanut allergens would discourage one of ordinary skill in the art from attempting to substitute them into methods that have only been described for tamer antigens such as isolated microbial antigens and non-anaphylactic allergens. Furthermore, as a consequence of the known risks that are associated with accidental exposure to anaphylactic peanut allergens, Appellant respectfully submits that one of ordinary skill in the art would have very little expectation that the substitutions would lead to successful methods of treating allergies to anaphylactic allergens.

Regarding heat-killing step (b), Applicant respectfully notes that the teachings of Yeung are not generalized to all bacteria as the examiner suggests. Instead, the teachings are very specific, namely that when heat-killed *Listeria monocytogenes* (HKL) is mixed with the keyhole limpet hemocyanin antigen (KLH) it acts as an adjuvant that can bias an allergic reaction towards a Th1-type response (e.g., see abstract). There is some discussion of mixing HKL with other antigens including allergens; however, there is no teaching or suggestion of incorporating KLH or other antigens *within* heat-killed *Listeria monocytogenes*. There is also no suggestion that the adjuvant effect can be generalized to other bacteria, let alone *E. coli*. On page 9 of the office action, the examiner refers to page 4151, column 1 and states that "Yeung et al. further teach heat-killed bacteria rather than live bacteria are effective in reducing antigen/allergen specific IgE synthesis." This description of Yeung's teachings is misleading. Indeed, the cited section of Yeung reads:

> Safety issues with *Listeria* may not be of major concern, since killed rather than live *Listeria* is effective; in addition, even live *Listeria* is not particularly invasive organism, and is a pathogen primarily in immunosuppressed patients or in the setting of pregnancy.

In contrast to the examiner's statement, Yeung does not teach anything about bacteria generally – the teachings are limited to *Listeria*.

Further, Applicant respectfully notes that when Yeung describes mixing heat-killed *Listeria* with allergens the discussion is limited to the types of mild allergens that are currently

treated by allergen immunotherapy (i.e., by increasing exposure to allergen extracts). Indeed, on page 4151, they state:

> The effectiveness of HKL as an adjuvant in reducing Th2-dominated immune response and reducing Ag-specific IgE synthesis suggests that it may be clinically useful in the treatment of disease caused by heightened allergen-specific Th2 response, such as allergy and asthma. *Allergen immunotherapy, which is currently performed by vaccination with aqueous extracts of allergen is used as an effective therapy for these two diseases* [...] although treatment failures are frequent (emphasis added).

Applicant respectfully submits that as was the case with substitution step (a) above, the potent immunological nature of anaphylactic peanut allergens would discourage one of ordinary skill in the art from attempting to substitute the peanut allergens of the '978 publication into the Yeung methods that have only been described for tamer antigens such as KLH and non-anaphylactic allergens. While allergen immunotherapy with aqueous extracts of allergen has shown efficacy for mild allergens (e.g., allergens from pollens and animal dander), initial trials with the more potent peanut allergens demonstrated an unacceptable safety:efficacy ratio (e.g., see Sampson, *J. Allergy Clin. Immun.* 90:151-152, 1992; Oppenheimer et al., *J. Allergy Clin. Immun.* 90:256-262, 1992; and Nelson et al., *J. Allergy Clin. Immun.* 99:744-751, 1997). Thus, as a consequence of the known risks that are associated with accidental exposure to anaphylactic peanut allergens, Applicant respectfully submits that one of ordinary skill in the art would have had very little motivation to make the substitution, let alone the expectation that the substitution would lead to successful methods of treating allergies to the anaphylactic peanut allergens of the '978 publication.

Finally, applicant respectfully submits that the examiner's obviousness arguments are based on improper hindsight reconstruction. It is imperative that the invention be viewed as it would have been perceived by those of ordinary skill in the art *at the time the invention was made*. The examiner must demonstrate that the person skilled in the art would have selected and combined the references to produce the claimed invention *without the advantage of hindsight or knowledge of the invention*. Here the examiner is attempting to combine three references that point in variety of directions but not towards the claimed invention. While hindsight is tempting it must be avoided, otherwise the test for obviousness will lose all meaning.

Based on the foregoing it is apparent that the combination of the '799 patent, the '978 publication and Yeung fails to establish a *prima facie* case of obviousness. The examiner's rejection of claims 34-36 and 38-44 under 35 U.S.C. § 103(a) in light of these references should therefore be removed.

Rejection of claim 41 for obviousness

Claim 41 was rejected under 35 U.S.C. § 103 as being unpatentable over the '799 patent in view of the '978 publication and further in view of U.S. Patent 5,834,246 ("the '246 patent"). The '246 patent is a secondary references that was cited solely as teaching elements or limitations that are present in dependent claim 41. Thus, the '246 patent was cited as teaching a composition comprising *E. coli* with an allergen that is located within the *cytoplasm*. The examiner does not point to any teachings in this secondary reference that would remedy the deficiencies in the combination of the '799 patent in view of the '978 publication that were noted above. Accordingly, this rejection should also be removed for the same reasons as above.

Conclusion:

For the reasons presented above, it is submitted that the examiner's rejections have been overcome and thus that the amended claims are allowable. If the examiner feels that a telephone interview would expedite the prosecution of this case towards allowance she is invited to contact the undersigned at 617-248-4793. In addition, please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,

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